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PREVALENCE OF GASTROESOPHAGEAL REFLUX DISEASE AMONG DIABETIC PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a common comorbidity among diabetic patients, but its prevalence and associated risk factors remain unclear. This systematic review aimed to determine the prevalence of GERD among diabetic patients and explore potential risk factors associated with this comorbidity.

Methods: A comprehensive search of PubMed, MEDLINE, Embase, Scopus, and Cochrane Library was conducted to identify relevant studies. Observational studies (cohort studies, case-control studies), cross-sectional studies, and systematic reviews/meta-analyses reporting on the prevalence or risk factors of GERD among diabetic patients were included. Data extraction and synthesis were conducted following predefined protocols.

Results: A total of 956 studies were initially identified, with 14 full-text articles reviewed. Eight studies met the inclusion criteria and were included in the systematic review. The prevalence of GERD among diabetic patients ranged from 16% to 48.7% across studies, with considerable variability observed. Some studies found significant associations between GERD and demographic factors such as gender and age, while others did not. Inconsistencies were also observed in the association of GERD with diabetic complications, duration of diabetes, and metabolic factors. Variations were noted in the impact of peripheral neuropathy on GERD-related complications, highlighting the complexity of this relationship.

Conclusion: This systematic review provides insights into the prevalence and risk factors of GERD among diabetic patients. The findings underscore the need for further research to elucidate the underlying mechanisms and risk factors associated with this comorbidity. Understanding the relationship between GERD and diabetes mellitus is crucial for effective management and prevention strategies. Further studies with standardized methodologies and larger sample sizes are warranted to confirm these findings and guide clinical practice.

Introduction

Several gastrointestinal motility problems, such as gastroparesis and gastro-esophageal reflux disease (GERD), are mostly caused by diabetes mellitus (DM) [1-2]. Patients with type 2 DM often have obesity. Both obesity and gastroesophageal dysmotility, whether present alone or in combination, have a role in the development of gastroesophageal reflux disease (GERD) in diabetic individuals. Obesity causes high intraabdominal pressure, which may lead to hiatal herniation. This herniation is anatomically related to the loss of lower esophageal sphincter tone, which in turn causes acid reflux. On the other hand, neuropathy that accompanies hyperglycemia and DM may lead to gastroparesis and esophageal dysmotility, which in turn can induce GERD.

In addition, ghrelin and motilin hormone imbalance is brought on by diabetes or obesity. Esophageal dysmotility and gastroparesis are both caused by hormone imbalance [1]. Patients with GERD have worse living circumstances, less productivity, and disturbed sleep, and they are also at increased risk of developing esophageal cancer and Barret's esophagus [3–4]. But gastrointestinal problems of diabetes may be prevented and treated with lifestyle changes including eating smaller meals and keeping blood sugar levels under control [2].

In Saudi Arabia, 32.8% of the population has type 2 diabetes [5]. Type 1 diabetes mellitus cases in children and adolescents in Saudi Arabia in 2019 were 31.4 per 100,000 people [6]. The general population of KSA also has a high incidence of gastroesophageal reflux disease, which ranges from 28.7 to 45.4% [7-8]. People with diabetes have a higher incidence of gastroesophageal reflux disease (GERD) than the general population, according to a number of international research [9–10].

Any "symptoms or complications associated with regurgitation from the stomach and (or) the duodenum to the esophagus" is what's called gastroesophageal reflux disease (GERD). It has been linked to esophageal cancer and Barrett's esophagus. Acid reflux and sour regurgitation are common signs. Globally, GERD prevalence has been on the rise, and it has a significant impact on patients' quality of life via issues including sleep disturbances, metabolic abnormalities, and cardiovascular illness. There is substantial evidence from several studies that individuals with diabetes mellitus (DM) often have GERD symptoms. According to research conducted in 2008 by Wang et al. on 150 patients with type II diabetes mellitus in the United States, 40.7% of diabetics have GERD symptoms [11]. The prevalence of GERD symptoms in type II DM was 23% [12], according to a 2012 study by Hirata et al. that examined 66 Japanese outpatients with type II DM using the Frequency Scale for the Symptoms of GERD (FSSG). Furthermore, several gastrointestinal symptoms were responsible for 18% of erosive esophagitis in DM patients who had esophagogastroduodenoscopy (EGD), according to one Korean research [13]. Still, nobody knows for sure how common GERD is among Americans with type II diabetes.

The exact mechanism by which type II DM patients develop GERD remains unclear. The increased frequency of classic GERD symptoms in type II DM patients has led researchers to suspect a number of pathophysiological variables, including obesity, peripheral neuropathy, metabolic syndrome, and FBG. Recently, peripheral neuropathy in particular has been the focus of a great deal of study [11, 14]. Nevertheless, there is ongoing discussion over how the aforementioned variables influence the occurrence of GERD symptoms in people with type II diabetes. Numerous studies have shown that gastrointestinal (GI) symptoms are more common in diabetic individuals with neuropathy compared to those without [11, 15, 16]. On the other hand, Clouse and Lustman found no correlation between gastrointestinal symptoms in diabetes patients and neuropathy issues in 1989 [17]. Lee et al. (2011) demonstrated that the percentage of patients having classic GERD symptoms was not significantly different between the two groups of type II DM patients with and without neuropathy [14]. Further investigation into the causes of the increased prevalence of GERD symptoms in type II diabetic individuals is warranted.

Methods

Review Question

The systematic review aimed to determine the prevalence of gastroesophageal reflux disease (GERD) among patients diagnosed with diabetes mellitus. Specifically, it sought to identify the frequency of GERD occurrence in diabetic patients and explore potential risk factors associated with this comorbidity.

Search Strategy

A comprehensive search was conducted across relevant databases including PubMed, MEDLINE, Embase, Scopus, and Cochrane Library. Additionally, grey literature sources such as conference proceedings and relevant organizational websites were searched. The search was limited to articles published in English.

Types of Studies Included

Observational studies (cohort studies, case-control studies), cross-sectional studies, and systematic reviews/meta-analyses were included in this review. Studies reporting on the prevalence or risk factors of GERD among diabetic patients were considered for inclusion.

Participants

The review included studies involving adult participants (aged 18 years and above) diagnosed with diabetes mellitus.

Search Keywords

Keywords used in the search strategy included variations of the following terms: "gastroesophageal reflux disease," "GERD," "diabetes mellitus," "diabetes," "prevalence," "risk factors," "adults," and related Medical Subject Headings (MeSH) terms.

Study Selection Process

Two independent reviewers conducted the initial screening of titles and abstracts identified through the search strategy. Full-text articles of potentially relevant studies were then retrieved and assessed for eligibility based on predefined inclusion and exclusion criteria. Any discrepancies were resolved through discussion or consultation with a third reviewer if necessary.

Outcomes

The primary outcome of interest was the prevalence of GERD among diabetic patients. Secondary outcomes may have included the identification of risk factors associated with the development of GERD in this population.

Data Extraction and Coding

Two reviewers using a standardized data extraction form performed data extraction independently. Extracted data included study characteristics (e.g., study design, sample size), participant demographics, prevalence rates of GERD, risk factors, and key findings. Any discrepancies were resolved through discussion or consultation with a third reviewer.

Data Management

Data from included studies were managed using reference management software such as EndNote or Zotero. Duplicate records were identified and removed during the screening process. Extracted data were stored securely and accessible only to the review team to ensure confidentiality and data integrity throughout the review process.

Results

The initial search identified a total of 956 studies from PubMed, Embase, Cochrane Library, and CINAHL. There were some duplicates and 60 studies were screened based on their titles and abstracts. Of these, 14 full-text articles were reviewed, and only eight studies were eligible for inclusion in this systematic review (Figure 1).

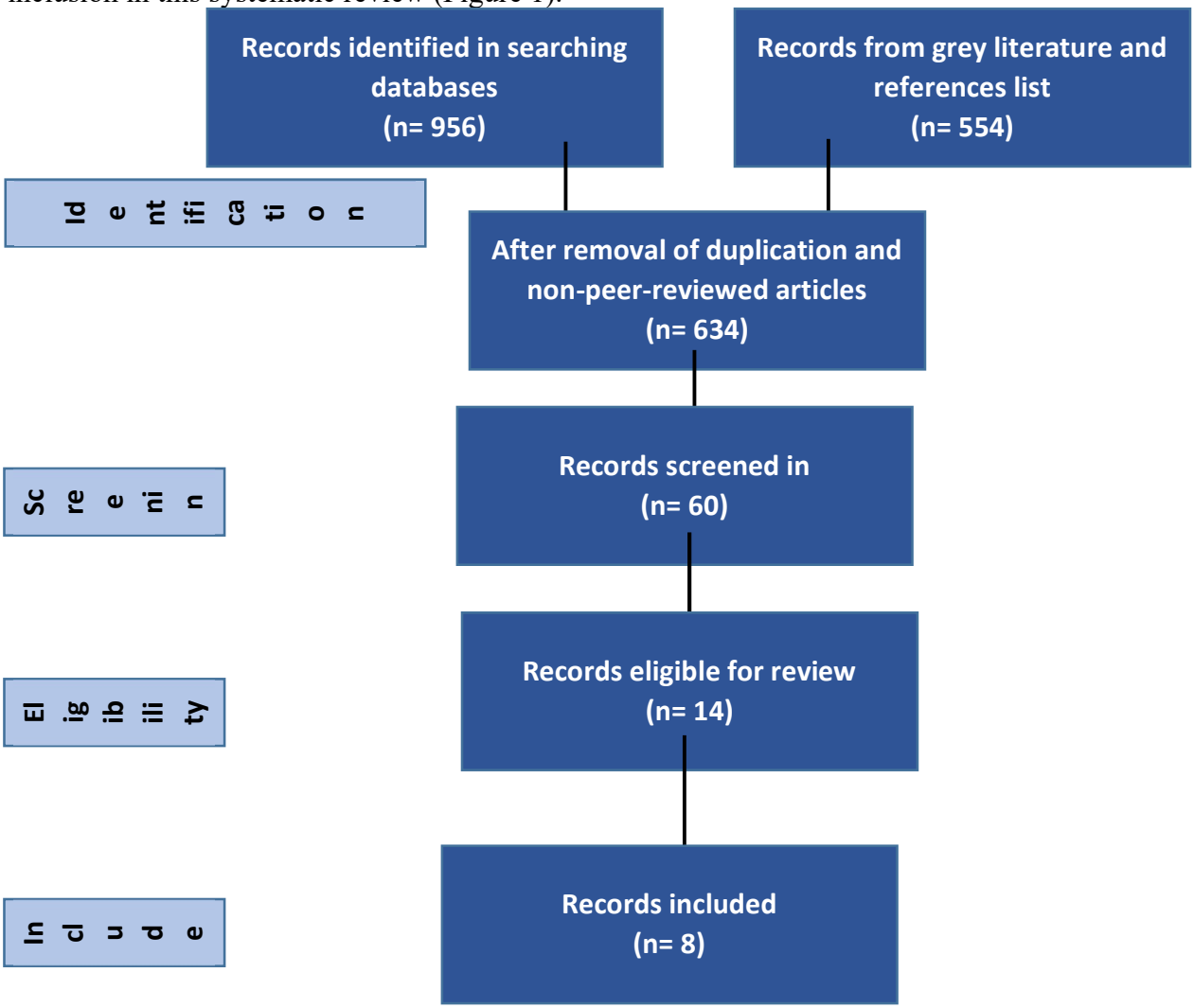

Figure 1: Flow chart of selection process

Among the included studies, one was conducted in KSA [18]. Between January and February 2019, 403 diabetic patients visited the outpatient clinics at King Khalid University Hospital, King Saud University Medical City, King Saud University; a tertiary hospital in Riyadh, Saudi Arabia. The researchers employed the GERD questionnaire (GerdQ) in this cross-sectional study. We divided the population into GERD and non-GERD categories using an 8 as our threshold score on the GerdQ. 44.9% of the population suffered from gastroesophageal reflux disease. Among the diabetic patients who had GERD, women made up 76.8% ($p<0.001$). Patients with gastroesophageal reflux disease (GERD) were somewhat heavier (32.04 vs 30.20 $p=0.006$) and somewhat older (mean age: 55.27, $p=0.038$) than those without GERD. Among those with GERD, 1.7% smoked, compared to 7.2% in the control group ($p=0.007$). Myocardial infarction was more common in people without GERD ($p=0.038$), but peripheral numbness and nephropathy were more common in patients with GERD ($p=0.023$ and $p=0.041$, respectively). Only being female ($p=0.013$) and being above the age of 65 ($p=0.007$) were shown to be independent risk variables for GERD in the multivariate analysis. The prevalence of gastroesophageal reflux illness in individuals with diabetes was 45%. Patients with diabetes and GERD tended to be older (>65 years) and female. Neither the GERD group nor the non-GERD group differed significantly from the other groups on any of the other measures (body mass index, smoking status, duration of diabetes mellitus, treatment plan, or diabetic complications) [18].

In China, a study conducted in Shanghai including 775 type II diabetes mellitus (DM) cases were examined for GERD using the Reflux Disease Questionnaire (RDQ). The prevalence of GERD among type II DM patients was 16%, with no significant differences observed in pathophysiological factors between GERD and non-GERD patients. This study emphasized the higher prevalence of GERD in type II DM patients compared to the general population [19]. Another study conducted in Indonesia, involved 101 diabetic patients assessed for GERD using the Indonesian GERDQ. The prevalence of GERD among diabetic patients was 29.7%, with spicy and high-fat diets identified as common dietary factors. Female gender was associated with GERD, while factors such as duration of DM, obesity, and uncontrolled diabetes showed no significant association [20].

In Pakistan a study conducted in Lahore involved 273 participants previously diagnosed with type II diabetes were evaluated for GERD using the GERDQ questionnaire. The prevalence of GERD was 48.7%, with regurgitation of stomach contents being the most common symptom. This study emphasized the need for awareness and early screening for GERD in diabetic patients [21]. A case-control study involving 258 T2DM patients and 184 healthy controls, found no significant difference in the prevalence of GERD between the two groups. Furthermore, GERD was not associated with diabetic complications or duration of diabetes in T2DM patients, highlighting the complexity of GERD's relationship with diabetes [22].

A descriptive cross-sectional study in Nepal, 191 type 2 diabetic patients were assessed for gastroesophageal reflux, revealing a prevalence of 40.84%. This study emphasized the common association of gastroesophageal reflux with diabetes in this population [23]. In another study, involving 95 type II diabetic patients, peripheral neuropathy was found to be an independent risk factor for erosive esophagitis but did not contribute to the presence of typical GERD symptoms. This study highlighted the differential impact of peripheral neuropathy on GERD-related

complications [24]. A Study conducted in Japan, explored the association between metabolic syndrome (MetS), serum adiponectin levels, and GERD symptoms in T2DM patients. The coexistence of MetS and low serum adiponectin levels was associated with a higher prevalence and severity of GERD symptoms, indicating potential synergistic effects of these factors [25].

In terms of methods, all studies employed cross-sectional designs except for study [22], which was a case-control study. The sample sizes varied across studies, ranging from 95 to 775 participants, and the studies were conducted in diverse geographical locations including Saudi Arabia, China, Indonesia, Pakistan, Nepal, and Japan. Different diagnostic tools were utilized to assess GERD, such as the GERD questionnaire (GerdQ), Reflux Disease Questionnaire (RDQ), and Indonesian GERDQ. Additionally, some studies conducted supplementary evaluations like face-to-face interviews, nerve conduction studies, electromyogram tests, and esophagogastroduodenoscopy. However, there were variations in the inclusion criteria regarding age, duration of diabetes, and exclusion of certain conditions like pregnancy and proton-pump inhibitor therapy.

In terms of results, the prevalence of GERD among diabetic patients ranged from 16% to 48.7% across studies, showcasing considerable variability. While some studies found significant associations between GERD and demographic factors such as gender and age [18, 20, 24], others did not [19]. Furthermore, there were inconsistencies in the association of GERD with diabetic complications, duration of diabetes, and metabolic factors across studies. Study [22] notably found no significant difference in the prevalence of GERD between T2DM patients and healthy controls, challenging previous findings. Additionally, variations were observed in the association between GERD and peripheral neuropathy, with some studies highlighting an increased risk of erosive esophagitis [24] while others found no significant impact on typical GERD symptoms [24]. These disparities underscore the complexity of the relationship between GERD and diabetes mellitus and suggest the influence of various factors such as geographical location, study design, and population characteristics. Table 1 summarizes studies characteristics. This table provides a concise overview of the study locations, designs, sample sizes, diagnostic tools used for GERD assessment, and any additional evaluations conducted in each study.

Table 1: Characteristics of studies included in the current review

Study	Location	Study Design	Sample Size	Diagnostic Tool	Additional Evaluations
AlTassan et al. [18]	Riyadh, Saudi Arabia	Cross-sectional	403	GERD questionnaire (GerdQ)	None
Sun et al. [19]	Shanghai, China	Cross-sectional	775	Reflux Disease Questionnaire (RDQ)	Laboratory data, face-to-face interview, nerve conduction study, needle electromyogram (EMG) test

Suwita et al. [20]	Indonesia	Cross-sectional	101	Indonesian GERDQ	None
Mehdi et al. [21]	Lahore, Pakistan	Cross-sectional	273	GERDQ	None
Ha et al. [22]	Not specified	Case-control	258 T2DM, 184 Controls	Physical examinations, laboratory tests, esophagogastroduodenoscopy	Medical records, long-term diabetes complications assessment
Mahato et al. [23]	Nepal	Cross-sectional	191	Not specified	None
Lee et al. [24]	Not specified	Cross-sectional	95	Electromyography (EMG), esophagogastroduodenoscopy	Peripheral neuropathy assessment, face-to-face interview
Hirata et al. [25]	Japan	Not specified	66	Questionnaire (Frequency Scale for the Symptoms of GERD - FSSG)	Measurement of visceral fat area

Discussion

This research set out to investigate how common GERD is and how it relates to diabetes mellitus (DM). Our data demonstrated that diabetes mellitus significantly increased the likelihood of esophagitis and GERD.

As per the Montreal definition [26], gastroesophageal reflux disease (GERD) is identified when the backflow of stomach acid causes serious symptoms and/or complications, such as reflux esophagitis, stricture, Barrett's esophagus, or esophageal adenocarcinoma, and when the condition is further classified as either an esophageal or extra-esophageal syndrome. Heartburn and regurgitation are the primary symptoms experienced by individuals with GERD [27]. Some forms of gastroesophageal reflux disease (GERD) include erosive esophagitis and endoscopy-negative reflux disease (sometimes called non-erosive reflux disease). According to reports, one of the reasons why GERD causes may be hard to pin down is because people often mix up reflux esophagitis with non-erosive reflux illness [26]. The fundamental mechanism of gastroesophageal reflux disease (GERD) remains unclear, despite the fact that reflux of intragastric contents is established as the cause. Age, gender, BMI, weight, level of alcohol intake, and smoking are among the many variables linked to gastroesophageal reflux disease (GERD) [28–31].

Common esophageal dysfunction in diabetic patients includes decreased amplitude of esophageal contractions, fewer peristaltic waves, slower peristalsis, lower pressure in the lower esophageal sphincter, and abnormal gastroesophageal reflux [32–34]. Not only does GERD (abnormal gastroesophageal reflux) lower patients' quality of life, but it also raises their chance of developing esophageal adenocarcinoma [35]. In GERD, the lower esophageal sphincter temporarily relaxes,

which is the dominant mechanism. Obesity and excess body fat are significant risk factors for gastroesophageal reflux disease (GERD), according to classic science. Several variables, such as an elevated intra-abdominal pressure, an increased gastroesophageal sphincter gradient, and the prevalence of hiatus hernia, have led to the notion that obesity may generate GERD symptoms [36]. Particularly among individuals who suffer from type 2 diabetes, there are diabetic patients who are overweight. There may be a correlation between DM and GERD for this reason. Most diabetic patients with esophageal dysfunction also exhibit signs of peripheral motor or autonomic neuropathy, leading some to speculate that autonomic neuropathy, particularly vagal nerve damage, is a major contributor to this dysfunction but leaving the exact pathophysiology of esophageal dysfunction in DM patients unknown. Moreover, erosive esophagitis might be exacerbated by diabetic autonomic neuropathy, which delays stomach emptying [37].

There is currently no agreed-upon understanding of the link between diabetic autonomic neuropathy and esophageal dysfunction, despite several reports in the scientific literature. Typically manifesting 5–10 years after diabetes starts, diabetic neuropathy may occur at any point in time when blood glucose levels start to rise [38]. Damage to both the efferent and afferent nerves occurs simultaneously in DM, which is why many patients have neuropathy in the absence of gastrointestinal symptoms [39]. As a result, some diabetic patients may not have specific symptoms of reflux, making it difficult to get an accurate diagnosis of esophageal dysfunction based on symptoms alone [40,41]. There is evidence from earlier research that the length of time a patient has had type 2 diabetes contributes to their gastrointestinal (GI) symptoms, as problems are more common in people with longer illness durations [41,42]. Reports indicate that a higher prevalence of symptomatic GERD is associated with diabetic retinopathy, neuropathy, and nephropathy [43]. Consequently, avoiding GERD in type 2 diabetes patients requires keeping to a healthy weight and an appropriate HbA1c level.

The results of a meta-analysis that took into account regions of the world revealed that GERD and DM were associated in both the Asian and Western subgroups, although only the former achieved statistical significance [44]. As a major clinical concern in Western nations, GERD affects 14% to 24% of people on a weekly basis, and the frequency has lately risen to almost one-third of the adult population [45]. Asia is a region where gastroesophageal reflux disease (GERD) is on the rise; over 10% of the population there suffers from acid regurgitation and/or heartburn symptoms on a weekly basis [28,46]. Eastern and Western cultures seem to have different GERD natural histories and clinical presentations because to ethnic distinctions [47]. Potential causes of these ethnic variances include variations in genetics, a high incidence of Helicobacter pylori infection, dietary variations, and changes in parietal cell mass and stomach acid output [48].

Is there an age-related rise in the incidence and prevalence of GERD symptoms? This is not yet known [29]. While some cross-sectional studies failed to find a link between the two, others demonstrated that erosive esophagitis was more common as people became older [49,50]. Our research confirms previous findings linking GERD with advancing age. Although it is not known for sure, impaired esophageal motility in the elderly may be one of the factors that contribute to the increased percentage of severe esophagitis in this age group. A hiatus hernia increases the risk of gastroesophageal reflux disease (GERD) in both the elderly and the general population, although it is more common in the former. Furthermore, hiatus hernias tend to become larger with age [51]. An earlier research also found that esophagitis severity was correlated with hiatus hernia size [52].

Conclusion

This systematic review identified eight studies from diverse geographical locations investigating the prevalence and risk factors of gastroesophageal reflux disease (GERD) among diabetic patients. The prevalence of GERD among diabetic patients ranged from 16% to 48.7% across studies, highlighting considerable variability. While some studies found significant associations between GERD and demographic factors such as gender and age, others did not. Furthermore, there were inconsistencies in the association of GERD with diabetic complications, duration of diabetes, and metabolic factors. Variations were also observed in the impact of peripheral neuropathy on GERD-related complications. These findings underscore the complexity of the relationship between GERD and diabetes mellitus, suggesting the influence of various factors such as geographical location, study design, and population characteristics. This systematic review contributes to the understanding of GERD in diabetic patients and highlights the need for further research to elucidate the underlying mechanisms and risk factors associated with this comorbidity.

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